Movement Disorders
CLINICAL PRACTICE

CASE REPORT

Atypical Glutaric Aciduria Type I with Hemidystonia and Asymmetric Radiological Findings Misdiagnosed as an Ischemic Stroke

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Introduction

Glutaric aciduria type I (GA-I) is an autosomal recessive disorder related to glutaryl-CoA dehydrogenase deficiency, responsible for the elevation of urinary 3-hydroxyglutaric acid (3-OH-GA) and inconsistently of glutaric acid (GA).[1] Dystonia and striatal lesions follow a period of metabolic stress with an encephalopathic crisis, usually between three and 36 months.[2]

Case Report

We report on the second child of unrelated, healthy Caucasian parents, born following an uneventful pregnancy and living in Romania. He attained normal developmental milestones until eleven months when he was admitted to hospital for a scheduled inguinal hernia surgery, as reported by his parents. Following a preparing drip, he became hypotonic and hyporesponsive and consequently, surgery postponed. Twenty-four hours later, despite fever, diarrhea, and vomiting, the child was discharged following cefotaxime, colistin, and hydrocortisone hemisuccinate treatment; two days later, the child became unconscious, presented a possible seizure with eye rolling and left-sided weakness. After the episode, left hemiparesis installed with psychomotor regression of the developmental milestones. No diagnosis was made before the first MRI, which was performed at the University Hospital in Bucharest at the age of two. The MRI showed T2-weighted hyperintense putaminal signal alteration (right side prominent), which was diagnosed as an ischemic stroke.

Clinical Assessment

At age seven, the child was referred to our department for assessment of deep brain stimulation indication for dystonia and for treatment of spasticity distributed over the left hemibody, involving upper and lower limbs (see Supporting Video S1). Axial tone and cervical posture were normal. Mild learning disability was reported. Written consents were obtained from both parents for the genetic analysis and the publication.

Biochemical and Genetic Analysis

Urinary organic acid analysis performed by gas chromatography—mass spectrometry of trimethylsilyl derivatives revealed a slightly elevated excretion of glutaric acid (GA = 14 mmol/mol of creatinine, reference range < 5) and higher excretion of 3-hydroxyglutaric acid (3-OH-GA = 31 mmol/mol of creatinine, reference range < 5). Acylcarnitine profile exhibited an increase of glutarylcarnitine, both in plasma (= 2,5 μmol/L—reference range < 0.2) and urine (= 22 mmol/mol creatinine—reference range < 5). GA-I was confirmed by molecular analysis. The patient is a compound heterozygote for sequence variations c.257C > G (p.Ala86Gly) in exon 4, and c.1262C > T

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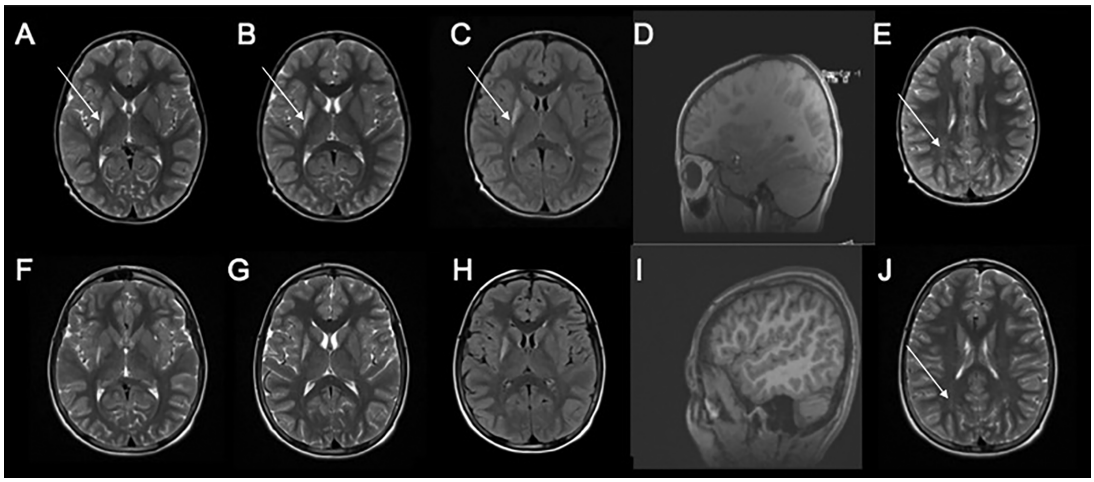

Figure 1 Panel A to E, brain MRI, 2012; A-B: axial T2w at basal ganglia level, C: FLAIR at another level within the basal ganglia to document the extent of BG abnormalities D: T1w sagittal to document the lack of enlarged Sylvian valley associated with classic GA-I; E: T2w at more dorsal level to document mild posterior white matter abnormalities. Panel F-J, brain MRI, 2017; the same sequences and similar levels, documenting stable radiological abnormalities

(p.Ala421Val) in exon 12 (inherited from his mother, previously described as pathogenic) 2 of GCDH gene (chromosome 19p13.2). The c.257C > G variant (inherited from his father, not described previously) concerns a highly conserved amino acid across species, and it is predicted as pathogenic by the sorting intolerant from tolerant (SIFT) algorithm.

Neuroradiological Data

Serial brain MRIs (Fig. 1) documented as main abnormality T2-weighted and FLAIR asymmetrical, right-side prominent putaminal hypersignal, with corresponding hyposignal in T1-weighted images. Frontotemporal hypoplasia and wide-open Sylvian valley encountered in GA-I were not documented but mild, posterior periventricular white matter changes.

Discussion

Normal urine or blood GA level is not suggestive for GA-I, but since some low excretors intermittently present with normal concentrations, it does not exclude it.[3] In contrast, elevated 3-OH-GA is highly suggestive for GA-I.[4] Further biochemical classification was proposed; a first group with high excretion of both 3-OH-GA, but higher GA, and a second group with increased 3-OH-GA that might go undetected by routine screening because GA excretion can be normal (Supporting Text S1).[1]

GA-I is heterogeneous also from a phenomenological and radiological perspective. No correlation of either genotype or biochemical phenotype with clinical and radiological pattern is known.[5–7] One hypothesis would be that the biochemical profile with residual GCDH activity will differently impact brain structure according to its maturation stages.

Related to basal ganglia abnormalities, generalized dystonia is a common feature in GA-I.[7] Classically, metabolic diseases are known to be responsible for bilateral clinical and radiological damage. Hemidystonia, due to asymmetric, mostly unilateral striatal lesions, is rarely related to GA-I; however, this diagnostic should not be missed.[8,9] Abrupt left-sided weakness and asymmetric striatal lesions could indeed correspond to an ischemic stroke in the territory of the lenticulostriate artery. Moreover, striatal necrosis from vascular ischemia and GA-I has identical neuroradiologic features.[10] The mechanisms underlying metabolic stroke are poorly understood. However, the same signal intensity alteration was documented in a patient with confirmed GA-I, but in whom installation of symptoms was insidious.[8] All in all, disentangling vascular from metabolically driven neurotoxic hypothesis in GA-I remains a challenge.[8]

Our GA-I case is remarkable since, untreated, the child developed an encephalopathic crisis with left dystonia and spastic hemiparesis associated with unilateral striatal necrosis. He did not progress further clinically and radiologically, potentially because of his low-excretion profile. However, 71% of the low excretors present with severe clinical phenotype.[1]

Conclusions

Unilateral clinical phenomenology and radiological pattern can relate to GA-I. Since a specific regimen is needed to prevent neurological damage during stressful medical or surgical events, a diagnosis should not be missed, and urinary organic acid and acylcarnitine analysis should be performed. Clinical, radiological, and biochemical follow-up add further insight into the complex

pathophysiology of GA-I. Newborn screening represents a major advance in preventing the severe evolution of the disease.

Author Roles

1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing the First Draft, B. Review and Critique.

D.D.: 1A, 1B, 1C, 3A
C.V.S.: 1B, 1C, 3B
C.A.: 1C, 3B
V.G.: 1C, 3B
I.D.A.R.: 1C, 3B
F.C.: 1B, 3B
T.R.: 1B, 3B
A.M.: 1B, 3B
N.L.: 1B, 3B
P.C.: 1C, 3B
L.C.: 1A, 1B, 1C, 3A, 3B

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Supporting Information

Supporting information may be found in the online version of this article.

Supporting Video S1. Sequence 1 (10 years old): sitting, standing, gait and lying conditions document left hemidystonia with involvement of upper and lower limbs and mild spasticity in the lower limb. Dystonic movements involving upper limb impair posture and are responsible of marked disability. Despite dystonic and spastic paresis of the left lower limb, gait remains autonomus. The child benefited from limited selective L5-S1 dorsal root rhizotomy and receives oral baclofen for treating spasticity. Sequence 2 (12 years old): no evident progression of dystonia compared to the first sequence.

Supporting Text S1. Biochemical, phenotype and radiological alterations.